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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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Paul Naik, Ph.D
Genentech Inc
1 DNA Way South
San Francisco, CA 94080

EXAMINER	
CANELLA, KAREN A	
ART UNIT	**PAPER NUMBER**
1643	

DATE MAILED: 08/11/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/995,693	SCHWALL ET AL.	
	Examiner	Art Unit	
	Karen A. Canella	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *51-60 and 64-70* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *51-60 and 64-70* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 61-63 have been canceled. Claims 51-60, 64-70 are pending and under consideration.

2. Sections of Title 35, U.S. Code not found in this action can be found in a previous action.

3. The rejection of claims 58, 67 and 68 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is maintained for reasons of record.

(B) It is unclear how claim 58 further limits claim 51. Claim 58 recites "said HGF receptor is the c-met receptor". By definition, the HGF receptor is synonymous with the c-met. Further the recitation of receptor relative to c-met in claim 58 and claim 59 is redundant because c-met is the receptor protein, not a receptor ligand. Applicant argues that usage in the filed encompasses such terms as "HGF and its C-met receptor and "Hepatocyte Growth Factor Scatter Factor (HGF-SC) and the C-Met Receptor". This has been considered but not found persuasive. In the examples provided the art is making reference to the difference between the Receptor (C-met) and the ligand (HGF). In the instant case , the above rejection is being maintained because claim 58, which specifies that the c-Met receptor, does not further limit claim 51, which recites HGF receptor. Applicant has not provided any evidence or arguments to refute the fact that the HGF receptor is synonymous with C-met.

(C) Claims 67 and 68 recite "binding ability" which is vague and indefinite because it is unclear if binding ability refers to simply the ability to bind the receptor, or if binding ability is intended to quantify the strength of the antibody interaction with the receptor, such as that quantitated as antibody affinity. For purpose of examination, all alternative will be considered. Applicant argues that the claims reciting "binding ability" are no vague and indefinite because it means simply the ability to bind to a target. This has been considered but not found persuasive. "Binding ability" in the analogous art, has two connotations, first, the ability to bind a substrate, which requires recognition of a specific structure on said substrate, and second, the strength of the interaction between the targeting ligand and the substrate. In the instant case it is unclear if "binding ability" refers to the binding at the same location within said substrate, i.e. the same

epitope which is bound by the monoclonal antibodies of ATCC-HB-11894 or 11895, or with the same binding affinity of ATCC-HB-11894 or 11895.

4. Claims 51-54, 58, 59, 64 rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Claim 51 is drawn in part to a method of treating cancer in a mammal comprising administering an effective amount of heptaocyte growth factor receptor antagonist to the mammal wherein said HGF receptor antagonist comprises a fragment of a chimeric, humanized or human antibody. When given the broadest reasonable interpretation, a hepatocyte growth factor receptor antagonists which is a "fragment" of an antagonistic antibody, need only comprise a single amino acid of the antagonistic antibody. Thus, the genus of "fragments" on which the instant method claims rely encompasses molecules that vary widely from the structures of the antagonistic antibodies that bind to HGF receptor. The specification provides a written description of antibody fragments which includes Fab, F(ab)'2 and Fv fragments of the antagonistic antibodies. This disclosure does not adequately describe the genus of "fragments" claimed because said genus includes molecules which only minimally comprise a single amino acid residues of the antagonistic antibodies. One of skill in the art would reasonable conclude that applicant was not in possession of the genus of "fragments" on which the instant method claims depend. It follows logically that if a genus of products is not adequately described, the method of using said products is not adequately described. Amendment of the claim to recite "HGF-receptor-binding fragments thereof" would overcome this rejection, as stated on page 2,section 5 (a) of the previous Office action.

Claim Rejections - 35 USC § 102

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

6. Claims 51, 53, 54, 58, 59 and 64 are rejected under 35 U.S.C. 102(e) as being anticipated by Rong et al (US 5,871,959).

The specific embodiments of the claims were recited in the previous Office action. Rong et al disclose a method of treating a tumor-bearing animal comprising administering a substance which inhibits the binding of HGF/SF with Met, wherein said substance can be an antibody or antibody fragment against HGF-F, an HGF/SF mimetic or a HGF-SF variant (column 3, lines 2-18, column 11, lines 49-55, column 12, lines 19-21) which fulfills the limitations of claim 51 and 59. Rong et al teach the treatment of sarcomas (abstract, last sentence) which fulfills the specific embodiment of claim 53, specifying sarcoma. Rong et al teach that Met is over-expressed in primary human sarcomas (column 26, lines 22-23) thus fulfilling the specific embodiment of claim 54, specifying over-expression of the HGF receptor. The disclosure of Rong et al fulfills the specific embodiment of claim 64 because the HGF-SF antagonists of Rong et al comprise a fragment of a chimeric, humanized or human antibody because when given the broadest reasonable interpretation, a fragment can be a single amino acid, and the structural limitations of a HGF receptor antagonists which comprises a fragment of a chimeric, human or humanized antibody is only limited by the possession of a single amino acid in common with the chimeric, human or humanized antibody.

Amendment of the claim to recite "HGF-receptor-binding fragments thereof" would overcome this rejection, as stated on page 2,section 5 (a) of the previous Office action.

7. The rejection of claims 51-54, 58-60, 64-66, 69 and 70 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-11, 15 and 16 of U.S. Patent No. 6,214,344 is maintained for reasons of record. Although the conflicting

claims are not identical, they are not patentably distinct from each other because the instant claims are obvious over the '344 claims.

Claims 51-53 are drawn to a method of treating cancer in a mammal comprising administering an effective amount of HGF receptor antagonist to the mammal wherein said antagonist comprises a chimeric, humanized or human antibody, or a fragment thereof. Claim 54 embodies the method of claim 51 wherein said cancer is accompanied by an increase in the level of HGF receptor activity in the mammal. Claim 58 embodies the method of claim 51 wherein the HGF-receptor is c-met. Claim 59 embodies the method of claim 52 wherein the antibody inhibits binding of human HGF to c-met. Claim 60 embodies the method of claim 51 wherein the antibody is monoclonal. Claim 64 embodies the method of claim 51 wherein the antibody is an antibody fragment.

Claims 65 and 66 embody the method of claim 51 wherein said antibody binds to the same epitope as the Fab fragment of the monoclonal antibody produced by the hybridoma ATCC HB-11894 and ATCC HB 11895, respectively. Claims 67 and 68 embody the method of claim 51 wherein said antibody has the binding ability of the Fab fragment of the monoclonal antibody produced by the hybridoma ATCC HB-11894 and ATCC HB 11895, respectively. Claims 69 and 70 embody the method of claim 51 wherein said antibody competes with the monoclonal antibody produced by the hybridoma ATCC HB-11894 and ATCC HB 11895, respectively.

Claim 1 of the '344 patent are drawn to a method of treating various forms of cancer comprising administration of an anti-HGF receptor antagonist antibody. Claims 2-5 specify cancers of the breast, colon and lung which anticipates the instant claims 52 and 53. Claims 6 and 8 of the '344 patent specify that the antibody is a monoclonal antibody and a Fab fragment of a monoclonal antibody, respectively, thus fulfilling the specific embodiments of the instant claims 51 and 60 as drawn to a fragment thereof, and a monoclonal antibody, respectively. Claim 7 of the '344 patent specifies that the antibody binds to c-met and claim 9 specifies that the antibody inhibits the binding of HGF to c-met, thus fulfilling the specific embodiments of the instant claims 58 and 59. Claims 10 and 11 of the '344 patent specify that the antibody is produced by the hybridoma of ATCC-HB-11894 and 11895, respectively, which anticipate the instant claims 65-70 because the monoclonal antibody would bind to the same epitope as that of a Fab fragment derived from it, and would also compete with other antibodies secreted from

ATCC-HB-11894 and 11895. Because it is unclear what limitations are concomitant with "binding ability", the antibodies secreted from ATCC-HB-11894 and 11895 anticipate the instant claims 67 and 68 because they would bind to the same epitope as the Fab fragment and would be expected to have the same binding affinity or a higher biding affinity than a Fab fragment.

8. The rejection of claims 51-56, 58-60 and 64-70 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-11, 15 and 16 of U.S. Patent No. 6,214,344 in view of Schlom.(In: Molecular Foundations of Oncology, 1991, S. Broder, Ed., pp. 95-134) is maintained for reasons of record.

Claims 55-56 embody the method of claim 51 wherein the antibody is chimeric or humanized. Schlom teaches that humanized or chimerized antibodies are useful in the clinical treatment of cancer in humans because said antibodies will avoid the HAMA response associated with the administration of murine antibodies to humans and allow for the multiple administrations of said antibody, which would be necessitated in the treatment of cancer. Schlom teaches that the HAMA response limits the effective dose of the antibody. Schlom teaches that in some instances the substitution of a human constant region has imparted an enhanced anti-tumor activity on a murine antibody (page 98, second column, second full paragraph to page 99, first column, line 4 and page 112, second column, second paragraph under the heading "Genetically Engineered and Chimerized Antibodies to page 116, second column, line 30).

It would have been prima facie obvious at the time the claimed invention was made to make a humanized or chimeric antagonistic anti-HGF receptor antibody in order to treat cancer in humans. One of skill in the art would be motivated to do so by the teachings of Schlom regarding the necessity of multiple administrations of a therapeutic antibody fro the treatment of cancer, and the teachings of Schlom regarding humanization of a murine antibody as a way of avoiding HAMA response against an administered antibody which limits the actual effective dose of said antibody.

9. The rejection of claims 57 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-11, 15 and 16 of U.S. Patent No. 6,214,344

in view of Schlom (In: Molecular Foundations of Oncology, 1991, S. Broder, Ed., pp. 95-134)as applied to claims 51-56, 58-62 and 64-70 above and in further view of the abstract of Marks et al., (J. Mol. Biol., 1991, Vol. 222, pp. 581-597) is maintained for reasons of record.

Claims 57 embodies the method of claim 51 wherein the antibody is human. Schlom teaches the potential use of combinatorial libraries which allows for the large-scale screening of Fab fragments from the murine antibody repertoire (page 123, first column, paragraph under the heading "Combinatorial Libraries"). Schlom teaches that feasibility studies will define the potential of such combinatorial libraries for the development of novel human antibodies (page 124, first column, lines 19-23). Schlom does not specifically teach obtaining a human antibody by the combinatorial library procedure.

The abstract of Marks et al teaches that a single large phage display library can be used to isolate human antibodies against any antigen by by-passing both hybridoma technology and immunization.

It would have been prima facie obvious at the time the claimed invention was made to make human antibodies which were antagonistic to c-met by means of a V-gene library displayed on phage. One of skill in the art would have been motivated to do so by the teachings of Schlom on the limitations of murine antibodies in human clinical studies and the suggestion of Schlom that human antibodies can be recombinantly expressed from a library, and the teachings of the abstract of Marks et al on the actually screening of human Fv fragments for a phage display library expressing both heavy and light chain human V-genes. One of skill in the art would be motivated to screen a library rather than obtain an antibody by hybridoma technology, because it is recognized in the art that hybridoma technology has not succeeded in masking cell lines which secrete human antibodies.

10. The rejection of claims 51-56, 58-60 and 64-70 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-5 and 11-19 of U.S. Patent No. 6,207,152 is maintained for reasons of record. Although the conflicting claims are not identical, they are not patentably distinct from each other because. the instant claims are obvious over the claims pf the '152 patent.

Claim 1 of the '152 patent is drawn to a method of treating cancer comprising administering an anti-HGF receptor antagonistic antibody which is monovalent. Claims 2-5 embody the method of claim 1 wherein the cancer is breast, pancreatic, colon and lung, respectively, which fulfill the limitations of the instant claim 52 and claim 53 which specifies a "carcinoma". Claims 12 and 13 specify that the HGF receptor is c-met and that the antibody inhibits the binding of HGF to c-met, respectively, which fulfills the specific embodiments of the instant claims 59 and 60. Claims 13, 14 and 19 of the '152 patent specifies that the monovalent antibody is a chimeric antibody having at least on domain of human origin, a humanized antibody, and a Fab fragment of a monoclonal antibody, respectively thus fulfilling the specific embodiment of claims 55, 56 with regard to a fragment of a chimeric or humanized antibody and the specific embodies of claims 60 and 64 which specify a monoclonal antibody and an antibody fragment. Claims 15 and 17 of the '152 patent are drawn to the method of claim 1 wherein said antibody has all the identifying characteristic of the Fab fragment of the monoclonal antibody produced by ATCC-HB-11894 and 11895; claims 16 and 18 embody the method of claim 1 wherein said antibody binds to the same epitope as the Fab fragment produced from the monoclonal of ATCC-HB-11894 and 11895, which fulfill the specific limitations of the instant claims 66-70.

11. The rejection of claims 51-60 and 64-70 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims of U.S. Patent No. 6,207,152 in view of Schlom (In: Molecular Foundations of Oncology, 1991, S. Broder, Ed., pp. 95-134) and the abstract of Marks et al (J Mol Biol, 1991, Vol. 22, pp. 581-597) is maintained for reasons of record.

Claim 57 embodies the method of claim 51 wherein the antibody is human.

Schlom teaches that the small size of single chain antigen binding proteins, which include Fv fragments, should improve the ability of the antibody to penetrate into tumor masses (page 122, second column, lines 15-17).

Schlom teaches the potential use of combinatorial libraries which allows for the large-scale screening of Fab fragments from the murine antibody repertoire (page 123, first column, paragraph under the heading "Combinatorial Libraries"). Schlom teaches that feasibility studies

will define the potential of such combinatorial libraries for the development of novel human antibodies (page 124, first column, lines 19-23). Schlom does not specifically teach obtaining a human antibody by the combinatorial library procedure.

The abstract of Marks et al teaches that a single large phage display library can be used to isolate human antibodies against any antigen by by-passing both hybridoma technology and immunization.

It would have been prima facie obvious at the time the claimed invention was made to make human antibodies which were antagonistic to c-met by means of a V-gene library displayed on phage. One of skill in the art would have been motivated to do so by the teachings of Schlom on the limitations of murine antibodies in human clinical studies and the suggestion of Schlom that human antibodies can be recombinantly expressed from a library, and the teachings of the abstract of Marks et al on the actually screening of human Fv fragments for a phage display library expressing both heavy and light chain human V-genes. One of skill in the art would be motivated to screen a library rather than obtain an antibody by hybridoma technology, because it is recognized in the art that hybridoma technology has not succeeded in masking cell lines which secrete human antibodies. Further, one of skill in the art would be motivated to select a Fv fragment because said fragment would be expected to penetrate the tumor mass more readily that the corresponding "whole" antibody.

8. Applicant states that a terminal disclaimer will be executed upon indication of allowable subject matter, however, claim rejections cannot be held in abeyance.

9. Applicant objects to the rejection of instant claims 52 and 53 which specify "carcinoma" by claims 2-5 of the '152 patent which specify breast, pancreatic, colon and lung cancers. This has been considered but not found persuasive. When given the broadest reasonable interpretation, claims drawn to breast, pancreatic, colon and lung cancers include "carcinomas" because it is well known in the art that carcinomas are the most frequent type of tumor in a human (see for example, Illingworth, Medical Hypotheses, 1986, Vol. 19, pp. 155-159).

Applicant argues that the examiner did not reiterate claim 15 and 17 of the '152 patent as reciting "biological characteristics" rather than "characteristics". This is not considered

persuasive because the examiners rejection was obviously not based on chemical, electrical or mechanical characteristics. Therefore the examiner was considering only "biological" characteristics.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen A. Canella whose telephone number is (571)272-0828. The examiner can normally be reached on 11 am to 10 pm, except Wed, Fri.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on (571)272-0832. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Karen A. Canella, Ph.D.
8/1/2005

Karen A. Canella
KAREN A. CANELLA PH.D
PRIMARY EXAMINER